Development of a Model for Integrated Pharmacokinetic and Pharmacodynamic Studies of Intravenous Anaesthetic Agents: Application to Minaxolone

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Summary. This study reports an approach to the investigation of new intravenous anaesthetic agents. Minaxolone (0.5%) was administered to healthy young adult volunteers in three different phases of study: (i) Subanaesthetic constant-rate infusion of 0.01 mg·kg⁻¹·min⁻¹ for 120 min; (ii) Subanaesthetic and anaesthetic infusion regimens of 0.05 mg·kg⁻¹·min⁻¹ for 60 min, followed immediately by 0.020 mg·kg⁻¹·min⁻¹ for 60 min; approximately four weeks later the same subjects received infusions of 0.01 mg·kg⁻¹·min⁻¹ and 0.015 mg·kg⁻¹·min⁻¹ respectively for the same period of time; (iii) Bolus injections of 10 mg and 40 mg over 1 min, at 2 h apart. Similar pharmacokinetic parameters were derived from all three different regimens, most notably characterised by high total body clearance (1.6 to 3.2 l·min⁻¹), correlating with rapid lucid clinical recovery of CNS function. Renal clearance was less than 0.5% of total body clearance, which was consistently 2 to 3 times the clearance of indocyanine green. Terminal half-life was short.

The subanaesthetic infusion regimen of minaxolone produced a sleep-like state from which subjects were rousable, obeyed commands readily and maintained verbal contact with investigators, while remaining amnesic throughout. This occurred at blood minaxolone concentration of 0.14 to 0.15 mg·l⁻¹. In the second stage, general anaesthesia was induced at a mean blood minaxolone concentration of 0.24 mg·l⁻¹ (SD 0.11). Intravenous bolus injections of 40 mg minaxolone invariably induced anaesthesia with mean blood concentrations of 0.49 mg·l⁻¹ (SD 0.29) 2 min postinjection. Onset of anaesthesia was very rapid, mean 55 s (SD 10), with a consistent duration of anaesthesia (mean 23 min, SD 3). Recovery was very rapid and lucid, without any tendency to lapse back into sleep again.

Generally, the incidence of adverse effects was greatest with anaesthetic bolus doses and least with subanaesthetic infusions. Whilst only mild excitatory movements were observed in 60% of subjects who received the subanaesthetic infusion, these increased in frequency and intensity with the anaesthetic infusions and occurred with the greatest severity in all subjects who received the 40 mg bolus injection. Tachycardia invariably was noted in all phases of study. A remarkably high incidence of respiratory upsets, in the form of tachypnoea, hyperventilation, apnoea, hiccoughs and laryngospasm, was observed with the 40 mg bolus dosage. Minaxolone, therefore, whilst possessing pharmacokinetic properties desirable of an IV anaesthetic agent, had disturbing clinical effects which may limit its clinical use. Using this approach, studies in only 15 volunteer subjects were successful in describing the pharmacokinetics, blood concentration-response relationships as well as the incidence and nature of side effects. On the basis of these data, it was possible to determine that the new drug, minaxolone, did not show sufficient promise to warrant further development. This methodology would seem to provide a useful model in the investigation of new intravenous anaesthetics to optimise patient safety and development costs.

Key words: minaxolone, anaesthesia; pharmacokinetics, pharmacodynamics

Introduction

Despite extensive research into new intravenous anaesthetic agents, thiopentone has remained the most popular IV induction agent since its introduction more than 40 years ago. In the intervening years, many drugs have been introduced to overcome the problems of delayed recovery observed when
thiopentone is used in sequential doses throughout a procedure. The advent of propanidid (Doenicke et al. 1968) suggested that very rapid and complete recovery from anaesthesia could be achieved with the use of a non-barbiturate having its duration of action limited by plasma enzymic biotransformation, rather than by redistribution from brain into other tissues, as occurs with thiopentone (Saidman 1974). However successful the concept, anaesthesia with propanidid was associated with an unacceptably high incidence of excitatory movements, post-operative vomiting and, particularly in poor risk patients, diminished the clinical usefulness of this agent. Other investigations have resulted in alphaxalone, a steroidal agent having a high therapeutic index and no cumulative effects (Child et al. 1971). This agent, combined with a similar, but less potent steroid, alphadolone acetate, was commercially formulated as Althesin (also known as Alfathesin or CT1341). Smooth induction of anaesthesia, rapid and lucid recovery, negligible emetic and venous sequelae (Hannington-Kiff 1972; Carson et al. 1972) were noted advantages of Althesin. Like all of the new drugs introduced, continuing experience showed that they are not more toxic than thiopentone, but that they produced different problems. Hypersensitivity reactions to Althesin have been reported with increasing frequency, although this drug has been available for less than 9 years (Dundee 1976). Like propanidid, formulation of the Althesin steroids also required solubilization in Cremophor EL, a polyethoxylated castor oil, which has been shown subsequently to produce anaphylactoid reactions in dogs (Child et al. 1971).

Attempts to obviate the use of this solubilizing agent by the manufacturers have resulted in the introduction of minaxolone (Glaxo Research Laboratories, Greenford, Middlesex, U.K.), a watersoluble steroid anaesthetic. Initial reports on the use of minaxolone in animals (Davis et al. 1979) and man (Aveling et al., 1979b; McNeill et al. 1979) have revealed favourable anaesthetic properties. Despite its early introduction into clinical trials in a considerable number of patients undergoing surgery, no Phase I clinical pharmacologic studies have been reported. Our studies were designed to provide basic clinical pharmacodynamic and pharmacokinetic data on minaxolone. Such studies are vital to rational clinical use of any new intravenous anaesthetic agent.

Thus, the purpose of the present study was (i) to describe the pharmacokinetic properties of minaxolone in healthy volunteers, i.e. in the absence of other drugs or surgical stress, at subanaesthetic and anaesthetic doses; (ii) to describe the objective and subjective clinical effects of the drug and correlate these effects with the minaxolone blood concentrations, and (iii) to examine the time course of effects on a psychometric test which correlates with CNS depression.

**Materials and Methods**

**Subject Selection and Preparation**

Fifteen healthy volunteer subjects (11 male and 4 female), aged between 19 and 32 years, and weighing between 53 and 84 kg, were studied. Prior to the study, a full physical examination, biochemical and haematological tests, and urine analyses were performed and found to be normal. Informed consent was obtained after a full explanation of the study protocol and potential risks. Subjects were advised to totally abstain from alcohol, sedatives and psychotropic agents for at least one week prior to study. After an overnight fast, each subject was familiarized with the personnel and equipment in the study room. A central venous line for blood sampling was inserted via an antecubital vein so that by measurement, its tip would have resided in the subclavian vein. A peripheral vein in the contralateral arm was cannulated for minaxolone and intravenous electrolyte solution infusion. Each subject was then allowed to rest for 1 h in the supine position before the test infusion was started.

**Infusion Regimens**

Preliminary studies performed in sheep (Gourlay et al. 1980) indicated that the total body clearance of minaxolone was high and principally hepatic. Other reports have indicated that the clearance of indocyanine green (ICG) correlates with other drugs that have a high hepatic clearance, e.g. lidocaine (Zito and Reid 1978) and propranolol (Branch et al. 1976). Hence the clearance of ICG was assessed in 13 of the 15 subjects prior to minaxolone administration as a reference point for each subject's capability for the elimination of a flow-limited substance.

A placebo 'dose' of intravenous electrolyte was studied for 30 min prior to each minaxolone administration. This was used to assess the nature and degree of psychogenic responses. Since there were no objective clinical or pharmacokinetic data on minaxolone in man, its administration was carried out in three stages involving increasing pharmacologic